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Donor-Derived Strongyloides stercoralis Infection in Solid Organ Transplant Recipients in the United States, 2009–2013

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Abstract

Infection with *Strongyloides stercoralis* is typically asymptomatic in immunocompetent hosts, despite chronic infection. In contrast, immunocompromised hosts such as solid organ transplant recipients are at risk for hyperinfection syndrome and/or disseminated disease, frequently resulting in fatal outcomes. Infection in these recipients may result from reactivation of latent infection or infection through transmission from an infected donor. We describe the Centers for Disease Control and Prevention's experience with seven clusters of donor-derived infection from 2009 to 2013. Six of the seven (86%) donors were born in Latin America; donor screening was not performed prior to organ transplantation in any of these investigations. Eleven of the 20 (55%) organ recipients were symptomatic, two of whom died from complications of strongyloidiasis. We also describe the New York Organ Donor Network (NYODN) experience with targeted donor screening from 2010 to 2013. Of the 233 consented potential donors tested, 10 tested positive for *Strongyloides* antibody; and 18 organs were transplanted. The majority (86%) of the donors were born in Central or South America. Fourteen recipients received prophylaxis after transplantation; no recipients developed strongyloidiasis. The NYODN experience provides evidence that when targeted donor screening is performed prior to transplantation, donor-derived infection can be averted in recipients.

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Introduction

Strongyloides stercoralis is an intestinal nematode found in tropical and subtropical regions worldwide, as well as temperate areas (1–3). The global burden of infection with *Strongyloides* is significant, with estimates of up to 100 million infected people (1,3). In the parasitic life cycle, filariform larvae penetrate human skin and are transported to the lungs through the bloodstream. They are then carried in respiratory secretions through the bronchial tree to the pharynx and swallowed, entering the small intestine where they can develop into adult worms. A distinct feature of the life cycle of *Strongyloides* is its ability to complete the entire cycle within one host, thereby leading to autoinfection, which can produce infection that can persist lifelong. In autoinfection, eggs that are produced by adult female worms within the intestine become rhabditiform larvae and subsequently filariform larvae. They can then penetrate intestinal mucosa or perianal skin, migrate to the lungs and begin the cycle again. Strongyloidiasis can present with diarrhea, abdominal pain, and skin manifestations but is often asymptomatic in immunocompetent individuals. However, in hosts with defects in cell-mediated immunity such as solid organ transplant (SOT) recipients, infection can result in hyperinfection syndrome and/or disseminated disease with fulminant and frequently fatal clinical presentations. Use of corticosteroids and immunosuppressive drugs are known risk factors for these conditions. Hyperinfection syndrome is defined by an increased production of larvae with parasites restricted to the pulmonary and gastrointestinal systems. Disseminated disease involves larval migration to other organs. Complications of disseminated *Strongyloides* include bacteremia and meningitis, with enteric Gram-negative bacteria gaining access to sites beyond the intestinal tract via disrupted mucosa or by migration with the larva themselves (4).

In addition to reactivation in chronically infected recipients, SOT recipients may acquire this infection through transmission from an infected donor (5–10). Previous screening recommendations have focused on preventing reactivation by testing for chronic infection in at-risk recipients by stool ova and parasite exams or IgG enzyme-linked immunosorbent assay (ELISA) antibody testing. Individuals at risk are identified by assessing potential exposure to the parasite in endemic areas based on country of origin and travel history (11–13). Some organ procurement organizations (OPOs) perform donor testing for certain pathogens of geographic significance (12), and current American Society of Transplantation (AST) guidelines recommend that evaluation for *Strongyloides* be strongly considered in transplant candidates and donors with epidemiologic risk factors or unexplained eosinophilia (14).

This article presents two clinical cases that highlight the salient aspects of the risk of strongyloidiasis in SOT recipients in the United States. We also describe the details of previously unpublished cases of donor-derived strongyloidiasis that were investigated by Centers for Disease Control and Prevention (CDC) and the experience of the New York Organ Donor Network (NYODN) which has been routinely testing at-risk donors since July 2010. To our knowledge, this is the first article to describe an OPO's experience with targeted donor screening. The findings provide further evidence to support recommending targeted donor and recipient screening for *Strongyloides* infection prior to SOT and may add to the evidence base for future guidelines.

Case Reports

Case 1

A 72-year-old Korean woman with chronic hepatitis C infection and hepatocellular carcinoma previously treated with chemoembolization underwent deceased donor liver transplantation. Posttransplant immunosuppression included tacrolimus, prednisone and mycophenolate mofetil; no induction therapy was administered. Two weeks later, the patient developed nausea, decreased appetite and weight loss that persisted for 2 months. She was hospitalized 3 months after transplantation with 3 days of diffuse abdominal pain, nausea and nonbloody emesis. Since her adherence to valganciclovir prophylaxis had been suboptimal due to intolerance, cytomegalovirus (CMV) disease was considered and intravenous ganciclovir (5 mg/kg every 12 h) was started. On hospital day 2, CMV DNA was not detected and ganciclovir was discontinued as there was no clinical improvement.

On the sixth hospital day, the patient developed altered mental status and hypoxia requiring supplemental oxygenation. Computed tomography scan of the chest revealed bilateral interstitial and alveolar pulmonary opacities. Empiric vancomycin and cefepime were initiated but blood cultures were negative. In addition to supplemental oxygen, the patient was treated with diuretics; after a right-sided thoracentesis was performed, her respiratory status improved. Pleural fluid studies were compatible with a transudative pleural effusion. On the eleventh hospital day, bronchoscopy was performed and revealed pulmonary hemorrhage and blood clots which were removed. Examination of the clot and bronchoalveolar lavage (BAL) fluid revealed larvae consistent with *S. stercoralis*, and ivermectin was administered orally (200 mcg/kg daily). However, the patient's mental status worsened and mechanical ventilation was required. Albendazole 400 mg twice daily was added the next day. Lumbar puncture was performed and examination of cerebrospinal fluid (CSF) revealed no white blood cells or organisms including *Strongyloides*; CSF cultures were negative. BAL cultures grew *Pseudomonas aeruginosa* and *Enterococcus faecalis*. The patient was treated with cefepime for 10 days for possible *Pseudomonas* pneumonia. The patient had limited bowel movements during the hospitalization, but on hospital day 25, examination of stool revealed *Strongyloides* larvae. Subsequent stool examinations were negative. Tracheal aspirates were also negative for parasites. Ivermectin and albendazole were discontinued on hospital day 26 after 13 and 12 days of therapy, respectively.

The hospital course was further complicated by need for tracheostomy and vancomycin-resistant *E. faecium* bloodstream infection. However, there was no further evidence of *Strongyloides* infection and she was eventually weaned off the ventilator and discharged to a rehabilitation facility on hospital day 64. Two years after transplant the patient was living at home with excellent liver graft function but has developed metastatic hepatocellular carcinoma.

Pretransplant testing for *Strongyloides* infection was not performed. Posttransplant serum that was obtained 2 weeks after clinical presentation tested negative for *Strongyloides* IgG. NYODN was contacted to explore the possibility of donor transmission. The two recipients of the donor kidneys were asymptomatic. One tested seronegative both pre- and posttransplant. The other tested negative posttransplant. Both kidney recipients were treated

with oral ivermectin after notification of the potential disease transmission. The donor was a 45-year-old man who died from subarachnoid hemorrhage due to a ruptured cerebral artery aneurysm. He was born in Guyana and lived there for over 30 years. Donor testing for *Strongyloides* infection was not performed at the time of organ procurement in this case. After the recipient was reported to be infected, donor serum subsequently tested positive for *Strongyloides* IgG by ELISA both locally and at CDC. The sample at CDC tested positive (>1.7 units/μL) at 4.98units/μL.

Case 2

The donor was a 49-year-old US-born homeless man who died from a subdural hematoma. Based on information obtained from his next of kin, he was a military veteran with no known international travel and donation occurred in Florida. Both of his kidneys were transplanted after death; no other organs were transplanted. Donor-derived infection was suspected when the left kidney recipient, a 61-year-old US-born female, presented with respiratory symptoms and was found to have *Strongyloides* parasites on microscopic examination of a BAL specimen. Pretransplant serum testing in the left kidney recipient was negative and stool examination was not performed. She was treated with oral ivermectin for 5 days followed by albendazole for 7 days and recovered without sequelae. The right kidney recipient was a 47-year-old female whose only notable complication posttransplant included chest pain diagnosed as chronic gastritis based on esophagogastroduodenoscopic biopsy. She was contacted after the left kidney recipient was found to have strongyloidiasis and received prophylaxis with a 2-day course of ivermectin followed by twice weekly ivermectin for 2 weeks. Both pre- and post-transplant serum in the right kidney recipient revealed no evidence of *Strongyloides* infection. Notably, during further investigation of these cases, a serum sample obtained from the donor was found to be strongly positive on *Strongyloides* antibody ELISA testing.

Methods

CDC investigations

CDC was notified of potential donor transmission of *S. stercorals* by the United Network for Organ Sharing or direct physician request for parasitic disease consultation after symptomatic disease was identified in SOT recipients. Stored donor serum was tested retrospectively for evidence of *Strongyloides* infection. Pretransplant serum specimens from the SOT recipients were requested to be sent to CDC to distinguish possible reactivation of chronic infection from newly acquired, donor-derived infection. The donor and recipient specimens were tested using the crude antigen (CrAg) ELISA (15–18). This quantitative validated assay has a sensitivity of 96% and a specificity of 98%. All reactions of ≤1.7 units/μL were considered negative and all reactions of >1.7 units/μL were considered positive, indicative of infection with *S. stercoralis* at some indeterminate point in time. This assay has demonstrated a good correlation between declining serological titers and cure (16).

NYODN screening protocol

Based on the recommendation of the NYODN Infectious Diseases Workgroup, NYODN began targeted screening of potential donors for *Strongyloides* in July 2010. All consented

deceased donors' next-of-kin were interviewed using a comprehensive medical-social questionnaire. This questionnaire includes questions to assess risk for infectious diseases and questions about travel history. Donors who have lived in the following areas for any period of time were tested: southeastern United States, Mexico, Puerto Rico, the Caribbean, Latin America, South America, Sub-Saharan Africa, Asia, India, and Oceania. Donor testing for *Strongyloides* was performed at Jacobi Medical Center's Parasitic and Tropical Disease Laboratory using a recombinant antigen immunoassay, NIE ELISA (16,19). Transplant centers were informed that donor *Strongyloides* testing is pending and organ procurement was not delayed in these cases. Results were shared with all recipient centers as soon as available.

Results

Summary of CDC Investigations

From 2009 to 2013 the CDC assisted in the investigation of S. stercoralis infection transmission from seven organ donors (Table 1) (2,6,10,20) in the following states: Pennsylvania [2], New York [2], Nevada [1], Massachusetts [1], and Florida [1]. Three of the investigations were conducted in 2012. The majority (86%) of donors was male and the median age was 49 years (range: 24–58). Six of seven (86%) donors were born in Latin America; one donor was born in the United States and had no known international travel. Donor screening was not performed prior to organ procurement in any of these investigations.

Across the seven investigations, 11 of the 20 recipients were symptomatic (Table 2) including eight kidney recipients, one liver recipient, one heart recipient, and one kidney-pancreas recipient. The majority (55%) of these symptomatic recipients was male, and the median age was 59 years (range: 14–72). Eight recipients presented with gastrointestinal complaints (i.e. nausea, vomiting and/or diarrhea) and six with respiratory complaints including shortness of breath and respiratory failure requiring intubation. Recipient infections were most commonly diagnosed by stool or BAL microscopy. The median time from transplantation to diagnosis of infection was 13 weeks (range: 7–33 weeks). Two of these symptomatic recipients died from complications of strongyloidiasis, one as a consequence of *Strongyloides* hyperinfection and the other due to disseminated disease with central nervous system (CNS) involvement (6,10).

Nine recipients did not develop evidence of posttransplant infection at the time of their last follow-up visit with their physician (Table 2). These recipients included four liver recipients and five kidney recipients; half of the recipients were male and the median age was 49 years of age (range: 41–66). Seven of the nine asymptomatic recipients received ivermectin prophylaxis. Of the remaining two recipients who did not receive prophylaxis, one experienced cardiac arrest and died prior to the diagnosis of the index case with strongyloidiasis and the other one was lost to follow up prior to the diagnosis of the index case with strongyloidiasis.

NYODN screening experience

Of the 1103 potential donors who were consented for donation, 233 (21%) were tested for *Strongyloides* antibody prior to organ procurement. Of the 10 (4.3%) who tested positive, seven became organ donors and three were not medically suitable for donation. In total, 18 organs were transplanted into 18 recipients from these seven suitable donors (Table 3). Of the seven donors, the majority (71%) was male and the median age was 46 years (range: 19–66). Six (86%) of the donors were born in Central or South America, and one was born in the United States but had traveled toendemic countries. Among the 17 recipients with follow-up data, 14 recipients received prophylaxis and three did not. At the last follow-up, none of the recipients had developed strongyloidiasis.

Discussion

The NYODN screening experience provides evidence that when targeted donor screening is performed prior to SOT, donor-derived infection can be averted in recipients. Eleven of the 20 recipients (55%) receiving organs from seven donors in the CDC investigations were infected post-transplant compared to none of the 14 recipients who received prophylaxis after the identification of donor infection with *S.stercoralis* as part of the NYODN screening program. Screening of live organ donors offers the opportunity to treat donors who test positive prior to organ donation, which may decrease the potential for transmission of *Strongyloides* infection to recipients.

Case report 1 highlights the importance of adhering to targeted donor and recipient screening. Although the NYODN screening program began in 2010, the donor in this case report was not tested and therefore not identified as having strongyloidiasis which resulted in donor-derived infection in the liver recipient. NYODN added a checkpoint during their preallocation huddle to review the risk factors for *Strongyloides* on each donor to make sure testing is sent appropriately. Case report 2 illustrates the concern for the potential of autochthonous infection in the United States; the donor, in this case, was a homeless military veteran with no known international travel. Published studies as recent as the early 1980s confirmed evidence of soil-transmitted helminths, including *S. stercoralis* throughout Appalachia and the southern United States (21). Most recently in 2013, a cross-sectional study conducted in a rural community in southeastern Kentucky, reported evidence of *Strongyloides* infection in five of the 102 participants who agreed to be tested for the study (22). Of the five participants, none reported international travel to countries where *Strongyloides* is known to be endemic.

The pathogenesis of *Strongyloides* dissemination in chronically infected deceased donors is not well defined. Chronic carriers are thought to harbor the parasite in the small intestine and may be at risk for dissemination and hyperinfection when exposed to glucocorticoids (e.g. during resuscitation efforts or organ procurement) (23,24). Many deceased donors receive methylprednisolone as part of a preconditioning regimen prior to organ procurement which has been proven to stabilize the donor, allowing for an increased number of organs to be procured per donor (25). In some cases, steroids are given hours prior to organ procurement, which is not thought to be adequate time for dissemination of *Strongyloides* larvae; in these cases, it is possible that the physiologic cortisol surge that occurs with an

acute stress response may lead to dissemination days prior to organ procurement. Alternatively, a small number of *Strongyloides* larvae may be present in organs outside of the gastrointestinal tract in the absence of reported symptoms. Further research is needed to better understand the biology of this parasite to allow for more accurate assessment of at-risk patients.

The diagnosis of latent strongyloidiasis remains a challenge despite its potential clinical importance, especially before administering chemotherapy or immunosuppression in at-risk patients such as those from regions where this infection is endemic. Stool tests have very low sensitivity and a single stool examination will not identify more than 70% of positive cases due to the low numbers and intermittent release of the parasite in stool (26). Due to the limitations of direct methods of detection, the diagnosis of strongyloidiasis is often based on immunological methods.

These assays are frequently ELISAs to detect IgG antibodies directed against antigens of S. stercoralis. CrAg preparations or recombinant antigens are employed in these assays and have the advantage of a higher sensitivity when compared to parasitological methods (16). Despite its diagnostic utility, serological assays using CrAg preparations might overestimate the prevalence of disease. This can be due to cross-reactivity with other parasitic infections. As an example, the CDC CrAg assay has a sensitivity of 96% and specificity of 98%. The specificity dropped to 72% when sera from persons with other parasitic infections were tested; however, undetected or unreported Strongyloides infection could not be ruled out in these cases (unpublished CDC data).

S. stercoralis hyperinfection syndrome is associated with significant morbidity and mortality and can be prevented by early diagnosis and treatment (27). One to 2 days of ivermectin for treatment of asymptomatic *Strongyloides* infection was found to be adequate in nonimmunosup-pressed individuals (28). When donor-derived *Strongyloides* infection is considered in one recipient, it is necessary to assess the other recipients, and prophylaxis may be needed to prevent the consequences of possible transmission. To date, disease has not been reported in recipients who received prophylaxis based on suspected or proven donor infection although it is not possible to determine if transmission would have occurred in the absence of treatment. In recent cases, recipients have been treated with 2 sequential days of ivermectin (200 mcg/kg daily) with repeat therapy 2 weeks later (2) although there is currently no consensus prophylaxis recommendation. Following treatment, close monitoring of the recipient for signs of clinical disease is recommended. Serologic testing for posttransplant evidence of infection in SOT recipients is not reliable due to decreased sensitivity in the setting of immunosuppression as observed in case report 1.

In summary, comparison of the results of the NYODN screening program with the CDC investigations highlights the benefits of targeted donor screening in minimizing the risk of donor-transmitted strongyloidiasis. Our findings demonstrate the risks associated with unanticipated donor transmitted strongyloidiasis and the potential benefit of targeted donor screening. When organs are accepted from donors seropositive for *Strongyloides*, monitoring and treatment of recipients with ivermectin may improve outcomes. Additionally, the case reports discussed provide further evidence for the establishment and

importance of adherence to the current AST guidelines of targeted *Strongyloides* screening in all donors and candidates with epidemiologic risk factors or unexplained eosinophilia (14). Adoption of these recommendations by all OPOs and transplant centers may prevent the morbidity and mortality associated with strongyloidiasis in SOT recipients.

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Abbreviations

AST	American Society of Transplantation
BAL	bronchoalveolar lavage
CDC	Centers for Disease Control and Prevention
CMV	cytomegalovirus
CrAg	crude antigen
CSF	cerebrospinal fluid
CT	computed tomography
ELISA	enzyme-linked immunosorbent assay
NYODN	New York Organ Donor Network
OPO	organ procurement organization
SOT	solid organ transplant

UNOS United Network for Organ Sharing

Table 1

Donor demographics and characteristics in CDC investigations of *Strongyloides* infection in United States, 2009–2013

Investigation	Year	State	Age/Sex	Birth country	Duration of US residence (years)	Cause of death
1	2009	NY	55/M	West Indies	21	Head trauma in motor vehicle accident (MVA)
2	2009	NV	58/F	Honduras	Unknown	Respiratory failure due to asthma exacerbation
3[#2]	2010	PA	54/M	Dominican Republic	2.5	Head trauma secondary to gunshot wound (GSW)
4[#20]	2011	MA	46/M	Honduras	7	Trauma in MVA
5[†]	2012	NY	45/M	Guyana	14	Cardiac arrest, subarachnoid hemorrhage
6[‡]	2012	FL	49/M	United States	Unknown	Subdural hematoma
7[#6,10]	2012	PA	24/M	Puerto Rico	8	Head trauma secondary to GSW

[#]Published (references noted in superscript).

[†]Case report 1.

[‡]Case report 2.

Table 2

CDC investigations for donor-derived *Strongyloides* infections in SOT recipients in the United, 2009-2013

Investigation	Year	State of donation	Organ	Age/ Sex	State of transplantation	Birth country	Pretransplant testing	Infected post-transplant	Posttransplant symptoms	Symptoms	Mode of diagnosis	Time from transplant to diagnosis (wks)	Treatment	One-year patient survival	Time from transplant to death (wks)	Reported cause of death
1	2009	NY	Kidney	**40/F**	NY (NYC)	West ndies	Unavailable	Yes[1]	Yes	Gastrointestinal (GI)	EGD[2], Colonoscopy, and stool exam	33	Treated	Yes		
			Kidney	41/F	NY (NYC)	England	Positive	Yes[1]	No	N/A	Serology	41	Treated	Yes		
			Liver	58/M	NY (NYC)	Eastern Europe	Unavailable	No	No	N/A	N/A	N/A	Not Treated	Unknown		
2	2009	NV	Kidney	**68/M**	NY (NYC)	US	Negative	Yes	Yes	GI & Respiratory	Skin biopsy, BAL[3], gastric aspirate	14	Treated	No	17	Sepsis, *Strongyloides* hyperinfection
			Kidney	49/F	NV	US	Unavailable	No	No	N/A	N/A	N/A	Treated/IWDT[4]	No	35	Unrelated; no evidence of *Strongyloides* infection
			Liver	46/F	CA	Vietnam	Unavailable	No	No	N/A	N/A	N/A	Treated/IWDT	Unknown		
3[5]	2010	PA	Kidney	**53/F**	NJ	US	Negative	Yes	Yes	GI & Respiratory	Stool exam	10	Treated	Yes		
			Kidney	**39/F**	PA	US	Negative	Yes	Yes	GI & Respiratory	Tracheal aspirate, serum, and stool exam	10	Treated	Yes		
			Liver	58/M	PA	US	Unavailable	No	No	N/A	N/A	N/A	Treated/I WDT	Yes	113	Respiratory failure
4[5]	2011	MA	Kidney	**60/M**	MA	Kenya	Negative	Yes	Yes	GI	BAL, gastric aspirate, and stool exam	14	Treated	Yes		
			Kidney	**37/M**	MA	US	Unavailable	Yes[1]	Yes	GI	Stool exam	~14	Treated	Yes		
5[6]	2012	NY	Liver	**72/F**	NY	Korea	Unavailable	Yes[1]	Yes	Respiratory	BAL and stool exam	13	Treated	Yes		
			Kidney	45/M	NY	US	Negative	No	No	N/A	N/A	N/A	Treated/IWDT	Yes		
			Kidney	59/F	NY	US	Unavailable	No	No	N/A	N/A	N/A	Treated/IWDT	Yes		
6[7]	2012	FL	Kidney	**61/F**	FL	US	Negative	Yes	Yes	Respiratory	BAL	27	Treated	Unknown		
			Kidney	47/F	FL	US	Negative	No	No	N/A	N/A	N/A	Treated/IWDT	Yes		
7[5]	2012	PA	Heart	**59/M**	PA	US	Negative	Yes	Yes	Respiratory	BAL	7	Treated	No	11	Pneumonia; Disseminated strongyloidiasis with CNS involvement
			Kidney and pancreas	**64/M**	PA	US	Negative	Yes	Yes	GI	EGD and stool exam	10	Treated	Yes		
			Kidney	**14/M**	PA	US	Negative	Yes	Yes	GI	EGD and stool exam	11	Treated	Yes		
			Liver	66/M	PA	Unknown	Negative	Unknown	Unknown	N/A	N/A	N/A	N/A	No	<1	Undetermined; no evidence of *Strongyloides* infection

Symptomatic recipients in bold; N/A, not applicable.

[1] As pretransplant testing was positive or unavailable for these recipients, the possibility of reactivation rather than donor-derived infection cannot be ruled out.

[2] Esophagogastroduodenoscopy-obtained biopsy.

[3] Bronchoalveolar lavage.

[4] intervention without disease transmission.

[5] Previously published.

[6] Case report 1.

[7] Case report 2.

Table 3

Donor and recipient characteristics with pretransplant positive *Strongyloides* antibody testing in donors at NYODN, 2010–2013

Donor	Year	Age/Sex	Birth country	Duration of US residence (years)	Organ(s) transplanted	Recipient(s) Age/Sex	Prophylaxis given to recipient posttransplant	*Strongyloides* infection in recipient post-transplant
1	2011	66/F	Haiti	12	LI	68/M	No	No
2	2011	39/F	US[1]	Unknown	RK	62/F	Yes	No
					LI	63/M	Yes	No
3	2011	19/M	Mexico	4	RK	12/F	Yes	No
					LK	12/F	Yes	No
					LI	55/M	Yes	No
					HT	54/M	No	No
4	2011	46/M	Ecuador	20	RK	61/F	NA	NA
					LK	44/M	Yes	No
					LI	47/M	Yes	No
					HT	44/M	No	No
5	2012	45/M	El Salvador	8	RK	45/F	Yes	No
					LK	56/M	Yes	No
					LI	64/F	Yes	No
					HT	59/M	Yes	No
6	2013	59/M	Guyana	7	RK	34/M	Yes	No
					LI	53/M	Yes	No
7	2013	60/M	Jamaica	7	LI	52/M	Yes	No

NA, information not available; RK, right kidney; LK, left kidney; LI, liver; HT, heart.

[1]Travel to Jamaica, Haiti, Panama, Mexico.